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**United States Patent** [19][11] **Patent Number:** **6,011,040****Muller et al.**[45] **Date of Patent:** **Jan. 4, 2000**

[54] **USE OF TETRAHYDROFOLATES IN NATURAL STEREOISOMERIC FORM FOR THE PRODUCTION OF A PHARMACEUTICAL PREPARATION SUITABLE FOR INFLUENCING THE HOMOCYSTEINE LEVEL, PARTICULARLY FOR ASSISTING THE REMETHYLATION OF HOMOCYSTEINE**

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[52] **U.S. Cl.** ..... **514/258**

[58] **Field of Search** ..... 514/258

[56] **References Cited**

#### U.S. PATENT DOCUMENTS

5,334,535 8/1994 Schlingmann et al. .... 435/280

#### FOREIGN PATENT DOCUMENTS

595005 9/1993 European Pat. Off. .  
97/27764 1/1996 WIPO .

#### OTHER PUBLICATIONS

Resch (ed.), Risikofaktor Homocystein Daten-Fakten-Strateien [Homocystein Risk Factor—Data-Facts-Strategies], Gesellschaft für Medizinische Information ISBN 3-980 45 36-0-C. (1996).

Fortin et al., Clinical Biochemistry, 28(2):155-162, 1995.

Mills et al., Supplement Publication to the Ceres Form on Jun. 14, 1995, 1996, pp. 756S-760S.

Loehrer, F.M., Abstract from Arterioscler Thromb Vasc Bio., "Low whole-blood S-adenosylmethionine and correlation between 5-methyltetrahydrofolate and homocysteine in coronary artery disease", 16:6, Jun. 1996, pp. 727-733.

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[57] **ABSTRACT**

This invention relates to the use of tetrahydrofolates in natural stereoisomeric form for the production of a pharmaceutical preparation suitable for influencing the homocysteine level, particularly for assisting the remethylation of homocysteine. Clinical areas of application include all anomalies of the homocysteine level, particularly the prevention and treatment of cardiovascular diseases and the prevention of neural tube deficiencies. The present invention also relates to pharmaceutical preparations comprising at least one compound selected from the group consisting of 5-formyl-(6S)-tetrahydrofolic acid, 5-methyl-(6S)-tetrahydrofolic acid, 5,10-methylene-(6R)-tetrahydrofolic acid, 5,10-methenyl-(6R)-tetrahydrofolic acid, 10-formyl-(6R)-tetrahydrofolic acid, 5-formimino-(6S)-tetrahydrofolic acid or (6S)-tetrahydrofolic acid or pharmaceutically compatible salts thereof, together with pharmaceutically compatible active and adjuvant substances, for influencing the homocysteine level, particularly when a methylene tetrahydrofolate reductase deficiency exists, such as when thermolabile methylene tetrahydrofolate reductase exists for example.

**22 Claims, No Drawings**